Section of Pathology

President Professor Nicholas H Martin FRCP

Meeting November 17 1964

Opportunistic Infections

Professor W St C Symmers
(Laboratories of Histopathology, Charing Cross Hospital Group and Medical School, London)

The Concept of 'Opportunistic Infections'

When it was suggested to the Council of the Section of Pathology that one of this session's meetings should be about 'opportunistic infections', the resulting questions made it clear that the expression is by no means as familiar here as in the United States of America. What are 'opportunistic infections'? What is their importance? What organisms cause them? In what circumstances do they occur, and what are their manifestations? This symposium may not provide the answers to all these questions, but it is a welcome occasion to correct some misconceptions and to stress the often tragic importance of these infections. Knowledge of their variety and of the circumstances in which they occur makes it possible to understand the problems that they set the clinician and the pathologist. Their prevention, and failing prevention their early recognition and so the possibility of being able to treat them, may then be hoped for.

What are 'Opportunistic Infections'?

An opportunistic infection may be defined as a serious and usually progressive infection by a micro-organism that has limited (or no) pathogenic capacity under ordinary circumstances, and that has been able to cause serious disease as a result of the predisposing effect of another disease or of its treatment.

When the organism causing an opportunistic infection is one that can also cause infection in the absence of predisposing factors, the opportunistic infection is severer than the infection occurring without predisposition. Rapid, hæmatogenous dissemination of the infection is particularly frequent and characteristic – the predisposing factors not only lower the patient's resistance to the infection but they enable the infection to develop and progress to an extent that is not seen otherwise.

Use and misuse of the expression 'opportunistic infections': As the means of referring specifically to infective complications occurring in the circumstances defined, and caused by such organisms, the expression 'opportunistic infection' meets a terminological need, even though we may not find it a particularly attractive addition to our vocabulary. Once the concept that it relates to has become well known, we may be able to do without a special term to distinguish these infections from other infective complications of diseases and of treatment, such as terminal bronchopneumonia and the consequences of faulty asepsis when giving drugs parenterally. It will then be generally understood that infections belonging to the latter category are only part of the picture, and that infective complications may also appear in unexpected and unfamiliar forms and be caused by unfamiliar micro-organisms. Meantime, the concept that is so strikingly and succinctly expressed in the words 'opportunistic infection' still needs the help of this distinctive name to keep us in mind of the great practical importance of these potentially very dangerous complications.

Nomenclature can help to familiarize us with novel concepts only if it is used thoughtfully and precisely. If the expression 'opportunistic infection' is to have any value, its use must be confined to designating those infections that fall within the meaning of the definition given. It is not applicable to any infection, serious or trivial, simply on the grounds that the infection would not have occurred had there been no predisposing or precipitating cause. The essential characteristic of an opportunistic infection is that the causative organism is one that is at most but feebly pathogenic, and that is found to cause grave and widely disseminated disease only when other diseases or their treatment set aside the patient's defences or provide access to tissues that cannot effectively respond to the challenge. It is a travesty of the term to pretend that it is appropriate to such familiar infective complications as the carbuncle of the diabetic patient, the pneumococcal or streptococcal bronchopneumonia in the child with measles or the adult with

influenza, the recrudescence of tuberculosis in the starving, cryptococcosis in the course of sarcoidosis or Hodgkin's disease, and thrush in the marasmic baby or in the old man with prostatic enlargement and uræmia. It might as well be said that if there were no injury there would be no tetanus, no wound sepsis, no rabies, no cat-scratch fever, and therefore that these infections too should be considered opportunistic – with them, the infections like malaria, typhus, and trypanosomosis that are inoculated through the bite of an insect could drift into the ambit of the designation 'opportunistic'. Deliberately to suggest that such infections are anything other than diseases in their own right would be the grossest abuse of common sense and a contemptuous disregard of semantics.

Yet, the introduction of the term 'opportunistic infection' to the medical vocabulary may easily and unthinkingly result in just that sort of misuse, unless we guard against it. As doctors, we seem prone to give a ready welcome to any novelty within the sphere of our vocation. Medical history from far in the past up to the present day exposes this weakness in the uncritical extrapolation of such concepts as miasma, humours, contagion, diathesis, dysendocrinism, avitaminosis, reticulosis, collagen disease and autoimmunity. It is not the 'opportunistic infections' that are the novelty but the label that they have been given – we must not let the label lose its value through misuse that can only deny these serious diseases the attention that their gravity demands.

As far as I know, the earliest reference to infections or micro-organisms as opportunistic was made only ten years ago. Seeliger (1954), discussing pulmonary mycoses, wrote: '*Bei der Mehrzahl der angeschuldigten Pilze handelt es sich um ausgesprochene* Opportunisten, *die erst nach einer Störung des biologischen Gleichgewichts ihre schädliche Wirkungen enfalten*' – 'The majority of the fungi blamed [for these infections] are frank *opportunists* that disclose their harmful effects only after a disturbance of [the host's] biological equilibrium'. Utz (1962) has pointed out that it is teleological to attribute opportunism to a micro-organism. Nevertheless, the term 'opportunistic infection' is appropriate to the concept and describes it well, and its novelty may focus attention on these complicating infections.

What is the Importance of the 'Opportunistic Infections'?

The importance of 'opportunistic infections' is twofold: (1) They are often predisposed to by therapeutic measures that should heal, not harm. (2) They commonly cause, or at least accelerate, death.

Most patients who develop opportunistic infections are already mortally ill. But it is an important fact that not all the patients who die of opportunistic infections would have died of the disease that predisposed to the infection, or that required the treatment that did so. Although early recognition of complicating infections is most urgent in cases of diseases that are not themselves likely to be fatal, there is no justification for the argument that because a patient has advanced and ineradicable disease there is no need to recognize its complications.

In a remarkably large proportion of cases the presence of opportunistic infection is first discovered *post mortem*, and then often not before the microscopical examination of the sections. Diagnosis at this stage cannot be complete, for the complete diagnosis requires isolation of the causative organism. Insufficient clinical awareness of the occurrence and manifestations of these infections is largely responsible for this unsatisfactory state. If there is to be a reasonable chance of treating these infections successfully, early diagnosis is essential, and this is particularly true in view of the fact that comparatively few of the infections that occur in these circumstances have clearly defined treatment. Treatment must, inevitably, be experimental, and the opportunity to determine the *in vitro* sensitivity of the organisms concerned may save precious time.

What Organisms Cause 'Opportunistic Infections'?

Up to the present, discussions of 'opportunistic infections' have tended to be concerned almost wholly with opportunistic fungal infections. These were the subject of the International Symposium on Opportunistic Fungus Infections (1962), and the publicity that they have had during the last few years has, not surprisingly, left a widespread impression that it is fungi, and only fungi, that set up the serious infections that occur as complications of the use of modern drugs and other therapeutic advances. In fact, 'opportunistic infections' may be caused by bacteria, viruses and protozoa, as well as by fungi: examples of all these are included in the latter part of this paper.

The impression that lowering of the body's defences against infection by disease or drugs predisposes specifically to fungal infections is in part a result of the contemporary increase in interest in fungal infections generally. Hitherto, with a few exceptions such as actinomycosis and candidosis (moniliosis), the deep-seated fungal infections have not been so familiar to clinicians and pathologists as infections caused by other types of organisms. Today's growing awareness of the occurrence and manifestations of these

diseases is to a large extent a reflection of a true increase in their frequency. This increase, in its turn, is due in part to the higher proportion of our patients who have been in parts of the world where mycoses are prevalent that in Britain we regard as exotic, and in part to an increase in the incidence of some of our native mycoses (Symmers 1964). The larger number of cases of the latter is undoubtedly related to their 'opportunistic' occurrence as a complication of certain types of modern therapy. Deep-seated fungal infections also occur as 'opportunistic' complications of various other diseases (Symmers 1963), particularly systemic diseases of the lymphoreticular system, serious blood diseases and severe metabolic diseases.

In What Circumstances do 'Opportunistic Infections' Occur?

By definition, opportunistic infections occur as complications of other diseases or of therapeutic measures. The risk is greatest when diseases that predispose to these infections are treated with drugs or other measures that also predispose to them. These ætiological factors may be considered briefly:

(1) *Diseases as factors predisposing to 'opportunistic infections':* Any gravely debilitating disease predisposes to certain forms of infection by commonplace pathogens such as the pneumococcus, *Staphylococcus aureus* and *Candida albicans* – suppurative bronchopneumonia and oral thrush are classic instances. These are not 'opportunistic infections', for the organisms concerned are natural pathogens, and these complications are the types of infection that they ordinarily cause. In contrast, the 'opportunistic infections', caused by organisms with little or no natural pathogenic capacity, are complications mainly of diseases that specifically interfere with the means by which the body defends itself against microbial invasion – severe blood diseases (such as agranulocytosis and leukæmia) and systemic diseases of the lymphoreticular system (Hodgkin's disease, for example). 'Opportunistic infections' are also predisposed to by diseases that so alter the biochemical equilibrium of the body that the organisms concerned proliferate, invade and establish infection – severe and poorly controlled diabetes mellitus, renal failure and hyperemesis are examples. These and other diseases, localized and general, that predispose to infection, including 'opportunistic infection', have been summarized recently in the *Proceedings*, with particular reference to the development of deep-seated fungal infections (Symmers 1964).

(2) *Therapeutic measures as factors predisposing to 'opportunistic infections':* The role of drugs in predisposing to infections has been reviewed recently (Symmers 1965*b*). We are concerned here only with predisposition to 'opportunistic infections' as defined at the beginning of this paper, and it is pertinent to note that it is not only drugs but the use of radiotherapy that may have this effect. Indeed, what has brought 'opportunistic infections' particularly to our notice is the use of any form of therapy that has a tendency either to interfere with the mechanisms of defence against infection or to facilitate ingress of micro-organisms into the tissues. Therapeutic measures, and drugs particularly, are more frequently the precipitating cause of these complications than are the diseases that are their other ætiological factor.

Among drugs that predispose to infections by lowering resistance are corticotrophin and the corticosteroids, the cytotoxic drugs, and antibiotics, particularly broad-spectrum antibiotics. How drugs interfere with protection against infection is only partly known – the reduction in granulocytopoiesis that the cytotoxic drugs may cause is an obvious factor, and interference with the formation or action of antibodies as an effect of corticosteroid activity may be responsible for the failure of resistance when patients are under treatment with these hormones. The role of antibacterial antibiotics in predisposing to infection by resistant organisms has, to a certain extent, been exaggerated in the past: however, there is no doubt about their role in encouraging the overgrowth of *Candida albicans* in the large intestine, and elsewhere, by suppressing the bacteria that ordinarily prevent predominance of the fungus – given a massive proliferation of the latter, its chances of infecting superficial lesions and thence invading the tissues are greatly increased.

(3) *The synergistic or additive influence of disease and its treatment on the development of 'opportunistic infections':* When a disease that predisposes to 'opportunistic infections' is treated with drugs or other measures that themselves predispose to these complications, the risk of their development seems to be substantially increased. This is the more so when invasion of the tissues is facilitated by such procedures as intravenous infusion, lumbar puncture or surgery. The combined effect of these different predisposing factors is so hazardous that it cannot be safely disregarded in any case – the need for clinical vigilance is imperative.

What are the Manifestations of 'Opportunistic Infections'?

This question cannot be answered here, even in outline. In some cases it seems to be true that there are no recognizable clinical manifestations of the infection, and in considering the importance

of 'opportunistic infections' it has already been noted that their presence is commonly recognized for the first time at necropsy. However, when the clinical records are reviewed in retrospect, it is often possible to pick out observations that were probably indicative of the infective process, and experience shows that the proportion of cases diagnosed in life is appreciably bigger when the clinician and the pathologist are actively on the look-out for this type of complication.

Illustrative Cases

The rest of this paper comprises summary accounts of four illustrative cases, all of them unusual examples of 'opportunistic infection'.[1]

Case 1 (Symmers 1965*a*, Case 1; 1965*b*, Case 6)
A man, born in 1919, was treated for Hodgkin's disease from 1951 until his death in 1963. The treatment comprised courses of deep X-ray therapy and of various cytotoxic drugs (mustine, tretamine, chlorambucil, thiotepa and cyclophosphamide). In July 1960 acute widespread tuberculous lymphadenitis with massive mycobacteriosis of the affected nodes (*Mycobacterium tuberculosis*, human type) was successfully treated with streptomycin, isoniazid and sodium aminosalicylate. In December 1960 cryptococcal meningitis was successfully treated with amphotericin B. From June 1962 to April 1963 recurrent hæmolytic episodes necessitated treatment with prednisone. In April 1963, nine weeks before death, acute 'blast cell' leukæmia developed and was treated with methotrexate and dexamethasone. *Necropsy:* (1) Hodgkin's disease. (2) 'Blast cell' leukæmia. (3) Infections: (*a*) Staphylococcal pneumonia and pyæmia. (*b*) Severe oropharyngeal and œsophageal thrush; candida endocarditis of atheromatous aortic valve; septicæmic candidosis with multiple visceral lesions. (*c*) Aspergillus infection of a pulmonary infarct; septicæmic aspergillosis with multiple visceral lesions. (*d*) Phycomycetous infection of lungs, with pulmonary and meningeal phycomycetous thromboangiitis and necrotizing phycomycetous encephalitis. (*e*) Cryptococcal pneumonia. (*f*) Pneumocystis pneumonia. (*g*) Cytomegalovirus infection of bronchi and lungs. No cultures were made. The infections were recognized by the distinctive appearances of the lesions and of the parasites in histological preparations (all are illustrated in the fuller accounts of the case that are cited above). There was no evidence of tuberculosis *post mortem*. *Comment:* The only investigations of the plasma proteins during the illness were simple quantitative estimations of total albumin and total globulin; they were normal (the last investigation was three months before death).

[1]It is largely by coincidence that the predisposing disease in each of the cases mentioned here was Hodgkin's disease. A special interest in malignant diseases arising in the lymphoreticular system has meant that there are disproportionately many cases of these conditions among the records of 'opportunistic infections' in the laboratory

The multiplicity of infections – bacterial, fungal, protozoal and viral – is without precedent in the literature. It would be difficult to deny that their occurrence was a result of the combined effects on the body's resistance of Hodgkin's disease and the administration of cytotoxic drugs, X-ray therapy and corticosteroids.

Case 2 (Symmers 1965*a*, Case 21)
A white student, aged 24, who had lived for twenty-one years in California, USA, developed Hodgkin's disease while in England. Four months later, after X-ray therapy had proved ineffective, treatment with mustine was started. After six weeks he developed pneumonia, of which he died six weeks later.
Necropsy: (1) Hodgkin's disease. (2) Extensive pneumonic (Fig 1) and hæmatogenous visceral coccidioidomycosis.
Comment: The patient's 'geographical history' was not elicited until after his death. It was then learnt that he had had initial infection with coccidioidomycosis as a child. The nature of the fatal pneumonia was first recognized when sections of the lungs were examined histologically. Yeast-like organisms that had been found repeatedly in films and cultures of sputum during the terminal illness had been regarded as saprophytes and were not studied. They may have been the coccidioides.

It seems reasonable to assume that activation of the dormant coccidioidal infection was an 'opportunistic' consequence of the presence of Hodgkin's disease and its treatment with X-rays and mustine. Although progressive infection and hæmatogenous dissemination may occur in cases of coccidioidomycosis in the absence of obvious predisposing factors, this is infrequent (in the great majority of those who are

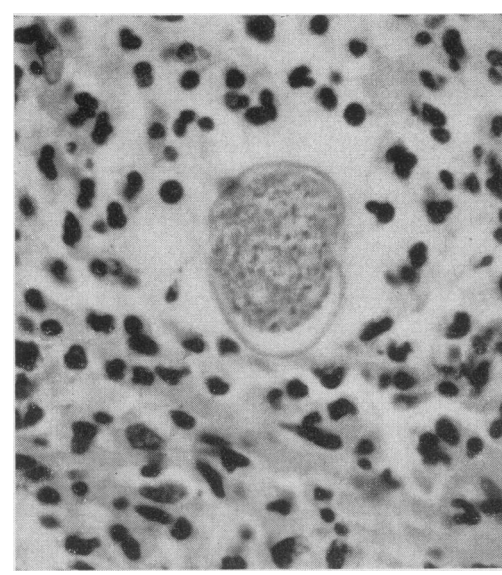

Fig 1 **Case 2** *Sporangium of* Coccidioides immitis *in pneumonic focus. Hæmatoxylin-eosin.* × *600*

infected in areas where the disease is endemic its manifestations are confined to the comparatively trivial effects of the self-limiting, initial lesion in the lungs). However, acute infection of the blood stream has been observed as a complication of corticosteroid therapy (Lipschultz & Liston 1964). A comparable effect has been observed in cases of histoplasmosis (Furcolow 1962).

Case 3 (Symmers 1965*b*, Case 16)
A young woman who had just completed an intensive course of deep X-ray therapy for widespread and advanced Hodgkin's disease refused to stay in hospital, but agreed to go to a convalescent home. For many months prior to the course of radiotherapy she had been treated with large doses of mustine and chlorambucil in alternating courses. On the day of her admission to the convalescent home there was an outbreak of food-poisoning due to *Salmonella newport*. Most of the patients and staff suffered a mild attack of enteritis and recovered quickly. The patient with Hodgkin's disease died eighteen hours after admission.
Necropsy: (1) Hodgkin's disease. (2) Heavy colonization of all organs and tissues by *Salmonella newport* (Fig 2). The necropsy was performed within twenty-five minutes of the patient's death.
Comment: Presumably the combined effect of Hodgkin's disease and the measures used in its treatment left the patient defenceless against the salmonella. It would have been interesting to know the white cell count and the plasma protein composition, but no data were available to the pathologist who carried out the post-mortem examination or have been obtainable from the hospital concerned.

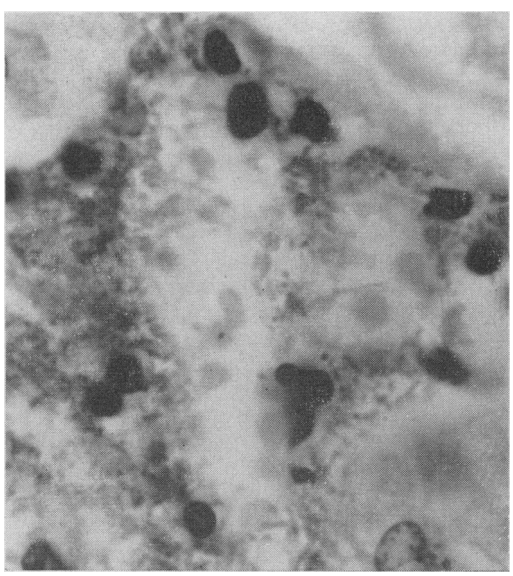

Fig 2 **Case 3** *The endothelial cells of this capillary in a kidney are packed with large numbers of bacilli* (Salmonella newport). *The organisms are also present in the cytoplasm of nearby fibroblasts or macrophages. Some lie free in the lumen of the blood vessel. Hæmatoxylin-eosin.* × *1,050*

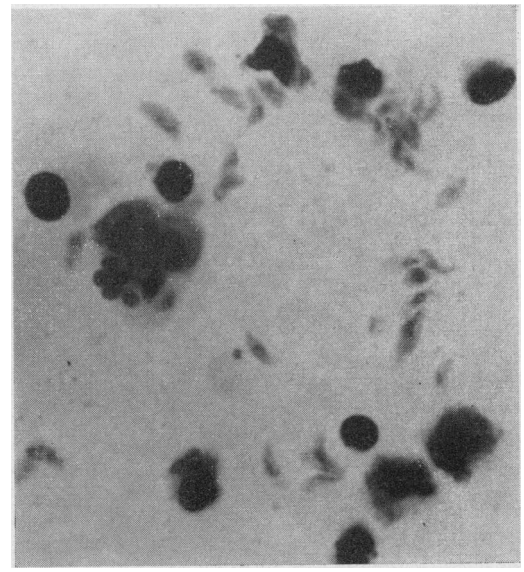

Fig 3 **Case 4** *Film preparation of uncentrifuged peritoneal fluid obtained by aspiration on the day before the patient died. Numerous crescentic toxoplasmas and the remnant of a toxoplasmic pseudocyst containing a cluster of spheroidal forms of the parasite are seen. The host cells include neutrophils, lymphocytes and mesothelial cells. Hæmatoxylin-eosin.* × *1,050*

Case 4 (Symmers 1965*b*, Case 17)
A man, aged 50, had been treated for Hodgkin's disease for four years with mustine and X-rays when the appearance of thrombocytopenic purpura necessitated treatment with hydrocortisone. Five months later, while still taking hydrocortisone, he developed toxoplasmosis (localized, histologically characteristic lymphadenitis, and a diagnostically rising titre in the 'dye test' and complement fixation test). The attempt to treat this infection with pyrimethamine was abandoned within five days because it precipitated severe thrombocytopenia. Four months after this, while he was still on treatment with mustine, X-rays and hydrocortisone, abdominal distension appeared rapidly, due to accumulation of fluid in the peritoneal cavity. Films of the fluid contained great numbers of toxoplasmas (Fig 3). The patient died a few days later. There was no necropsy.
Comment: Toxoplasmosis is not known to cause peritonitis in man. In the case described, this occurrence must be regarded as an 'opportunistic' effect, consequent on the therapy used and the underlying disease, and possibly precipitated by the administration of hydrocortisone.

Conclusions and Summary

'Opportunistic infections' – serious infections caused by micro-organisms that ordinarily are either harmless or of limited pathogenicity – are important in modern medicine, occurring either as complications of diseases that interfere with

the body's defences against invasion by potential pathogens or as a side-effect of drugs and other therapeutic measures. Their particular frequency as iatrogenous diseases has made them a danger common enough and grave enough to necessitate constant watch for their development when any patient is under treatment with corticosteroids, cytotoxic agents and broad-spectrum antibiotics, or with radiotherapy.

'Opportunistic infections' are often the immediate cause of death in cases of chronic debilitating disease, particularly cancer. In assessing their importance in cases of this sort it has to be remembered that they have to some extent taken the place of terminal bronchopneumonia as the closing stage in the course of the illness. Many patients with cancer nowadays live much longer than would have been the case before the introduction of modern advances in the treatment of neoplastic diseases; moreover, simple pneumonia in these patients is often not the danger that it was once, for it may be cut short and cured by giving antibiotics. Many of the micro-organisms that cause 'opportunistic infections' are resistant to drugs, or respond only to treatment with drugs, such as the antifungal antibiotic, amphotericin B, of which the side-effects are liable to be particularly dangerous in these chronically debilitated patients. It is sometimes the case, then, that there is nothing to be done to overcome an 'opportunistic infection'. As has been mentioned, this cannot be an excuse for failure to establish early diagnosis of the presence of such infections – their prevention, or their successful treatment, may provide the chance of bringing the patient's underlying disease under control and, at least in some cases, of restoring his health.

The four cases summarized in this paper include instances of infection by bacterial, fungal, viral and protozoal 'opportunists'. In one of the cases all four of these groups of organisms were represented, and no fewer than seven different types of organism were recognized at necropsy.

REFERENCES

Furcolow M L (1962) *Lab. Invest.* **11**, 1134

International Symposium on Opportunistic Fungus Infections (1962) *Lab. Invest.* **11**, 1017–1241

Lipschultz B M & Liston H E (1964) *Dis. Chest* **46**, 355

Seeliger H (1954) *Med. Mschr.* **8**, 692

Symmers W St C (1963) *Pat. pol.*, suppl. 1, 321

(1964) *Proc. R. Soc. Med.* **57**, 405

(1965*a*) In: Symposium on Medical Mycology (International Academy of Pathology, London 1964). Ed. C H Binford & F K Mostofi. Baltimore (in press)

(1965*b*) In: Drug-Induced Diseases – Second Symposium Organized by the Boerhaave Courses for Post-Graduate Medical Education, State University, Leyden. Ed. L Meyler. Amsterdam (in press)

Utz J P (1962) *Lab. Invest.* **11**, 1018

Dr H Stern
(*Virology Department, St George's Hospital Medical School, London*)

Human Cytomegalovirus Infection

The cytomegaloviruses are members of the herpesvirus group which is responsible for probably the majority of opportunistic viral infections. They are the prime examples of the group in this respect, since they have been recognized to cause disease almost exclusively in individuals with impaired immunity responses. However, there is increasing evidence that the clinical spectrum of cytomegalovirus infection is wider than previously believed.

Until a few years ago the diagnosis of cytomegalic inclusion disease was possible only by histological methods and was usually made unexpectedly at post-mortem. The histology is characterized by the presence of cytomegalic cells. These are very large cells with a large nucleus containing a prominent inclusion body. In stained tissue sections the inclusion body is typically surrounded by an unstained halo giving rise to the so-called 'owl's-eye' appearance. The recognition of cytomegalic cells in the urine provides a method, an insensitive one however, of diagnosis during life (Fetterman 1952). Nor is histological examination of tissues obtained by biopsy or at post-mortem always reliable for diagnosis, as cytomegalic cells can be scanty or absent even when virus is readily isolated from the same specimens (Hanshaw & Weller 1961, Weller & Hanshaw 1962, Stern *et al.* 1963). In the body the virus is predominantly epitheliotropic, although mesothelial cells are occasionally affected especially in adults. This is in striking contrast with the situation in tissue culture where the virus has been grown only in fibroblasts; the cytopathic effect is similar to that in the body with the formation of cytomegalic cells having large intranuclear inclusion bodies. Electron microscopy confirms that the virus belongs to the herpesvirus group by showing that the structure of its capsid is identical with that of herpes simplex virus (Smith & Rasmussen 1963, Wright *et al.* 1964). The capsid develops in the nucleus of the infected cell and subsequently collects an outer envelope from the surface membranes of the cell (Stern & Friedmann 1960).

On the basis of post-mortem studies two forms of cytomegalic inclusion disease have been recognized, disseminated and localized. The severest and most characteristic example of disseminated disease occurs in the newborn. These cases acquire their infections *in utero* and the clinical features, which are present at birth or appear shortly afterwards, include jaundice with hepato-